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Italian Journal of Vascular and Endovascular Surgery 2021 September;28(3):81-90
DOI: 10.23736/S1824-4777.21.01509-6

REVIEW

Arterial thrombosis: the obscure threat in COVID-19 pandemic victims

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ABSTRACT

INTRODUCTION: SARS-CoV-2 is a novel Coronavirus responsible for the current global pandemic resulting in an escalating number of cases and fatalities worldwide. There is a growing number of reports regarding patients presenting with acute limb ischemia due to thrombosis of all arterial beds. We conducted a literature review to identify and summarize the available data regarding the incidence of COVID-19 induced acute peripheral arterial thrombosis, potential pathophysiological mechanisms, clinical representation, diagnosis, surgical outcomes and limb salvage results.

EVIDENCE ACQUISITION: References for this review were identified through searches on PubMed, Ovid Medline, and Embase from December 1, 2019 to March 15, 2021 using relevant terms related to COVID-19. Reference lists of the articles were also searched. Thirty-six publications were deemed relevant for the purpose of this literature review.

EVIDENCE SYNTHESIS: An aggressive and timely medical therapy and surgical interventions should be performed to obtain positive treatment outcomes. Nevertheless, the absence of evidence-based protocols remains an obstacle for healthcare providers. Further quality research about SARS-CoV-2 infection with a focus on arterial thrombotic complications are needed to characterize arterial consequences of Coronavirus and to evaluate the necessity of therapeutic anticoagulation in COVID-19 patients with peripheral arterial occlusive disease or thrombophilia.

CONCLUSIONS: Healthcare providers should be aware of the manifestations of COVID-19 and a high index of suspicion should be maintained so that all can benefit from evidence of measures that have been found to be effective. Although previous reports also identified COVID-19 patients with limb ischemia, there is limited data on the clinical course and treatment.

(*Cite this article as:* Boneva BP, Dimova MP, Nikolov NK, Stoyanova BI, Ilchev BN. Arterial thrombosis: the obscure threat in COVID-19 pandemic victims. Ital J Vasc Endovasc Surg 2021;28:81-90. DOI: 10.23736/S1824-4777.21.01509-6)

KEY WORDS: COVID-19; SARS-CoV-2; Coronavirus; Thrombophilia.

Introduction

SARS-CoV-2 is a novel Coronavirus responsible for the current global pandemic resulting in an escalating number of cases and fatalities worldwide. As Coronavirus 2019 (COVID-19) continues to cause an immense burden on the global health care systems, it is crucial to understand the breadth of this disease process. All of the mechanisms in which COVID-19 affects the human body still remain unclear. Patients mainly present with upper and lower respiratory tract symptoms, complications such as cytokine storm and acute respiratory distress syndrome.[1]

COVID-19, the disease caused by the new Coronavirus, can cause lung complications such as pneumonia and, in the most severe cases, acute respiratory distress syndrome (ARDS). Sepsis, another possible complication of COVID-19, can also cause lasting harm to the lungs and other organs and systems in the human body. In cases of severe pneumonia, the lungs become filled with fluid and inflamed, leading to breathing difficulties. For some people, breathing problems can become severe enough to require treatment in hospital with additional oxygen supply or even a ventilator could be needed. The pneumonia that COVID-19 causes tends to take hold in both lungs. Oxygenation ability is thus limited. While most people recover from pneumonia without any lasting lung damage, the pneumonia associated with COVID-19 may be severe with all the complications mentioned above. Other

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outcomes are also very common. Thrombotic events range from acute pulmonary embolism in patients with COVID-19 pneumonia to arterial thrombosis and extremity ischemia, and the precise incidence of thrombotic events has yet to be determined.[2]

It has been reported that the viral infection can be responsible for venous and arterial thromboembolism,[1] however limited data is available regarding acute peripheral limb thrombosis, its predominant patient population and its surgical intervention outcomes. Despite the limited number of publications, case reports and case series, as well as prospective studies and meta-analysis in the vascular departments of multiple hospitals there is a growing number of unusual acute arterial thrombosis in young and otherwise healthy patients. Emerging evidence suggests that these severe and critical forms of COVID-19 are mediated, in part, by a hypercoagulable state characterized by micro- and macro-vascular thrombotic angiopathy.[3] Patients with severe cases of COVID-19 presented with significant elevation of D-dimer, prothrombin and fibrinogen levels, supporting our statement. Furthermore, systemic hyperinflammation with elevated proinflammatory cytokines (tumor necrosis factor, IL-6, IL-1beta) is associated with severe COVID-19 cases which contribute to intravascular coagulopathies.[4, 5] The common narrative suggests that COVID-19 is associated with a thrombosis of the microcirculation. In reality there is a growing number of reports all over the world of patients presenting with acute limb ischemia (ALI) due to thrombosis of aorto-iliac, femoro-popliteal and axillo-brachial segments.

There seems to be a substantial amount of evidence supporting venous thrombotic and thromboembolic events, in comparison to the few reports regarding acute arterial thrombosis in these patients.

Therefore, we conducted a literature review to identify and summarize the available data regarding the incidence of COVID-19 induced acute peripheral arterial thrombosis, potential pathophysiological mechanisms, clinical representation, diagnosis, surgical outcomes and limb salvage results.

Evidence acquisition

Search strategy

References for this review were identified through searches on PubMed, Ovid Medline, and Embase from December 1, 2019, to March 15, 2021, by a team of vascular surgeons from National Cardiology Hospital, Sofia, Bulgaria, using relevant terms related to COVID-19, SARS-CoV-2, 2019.nCoV, novel Coronavirus, endothelial dysfunction, endotheliitis hypercoagulability, immunothrombosis, arterial thrombosis, acute limb ischemia, peripheral thrombosis. Reference lists of the articles identified by this search strategy were also searched. Only articles published in English were included in this review. Thirty-six publications were deemed relevant for the purpose of this literature review.

Evidence synthesis

Pathophysiology/pathogenesis

The exact mechanisms causing acute arterial thrombosis (AAT) in COVID-19 patients still remain not fully understood. It seems that there are two main factors-endotheliitis and hypercoagulability, combined with prolonged immobilization of critically ill COVID-19 patients (completing the Virchow's triad) which are a plausible explanation for the mechanisms of arterial thrombosis (AT).

Thrombotic events developed even in patients without gross evidence of atherosclerosis which is an established precursor for AT.[3]

It is known that SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells (EC). This invasion results in systemic vasculitis and decreases immune function.

Other receptors/facilitators on the surface of human cells have been suggested to mediate the entry of SARS-CoV-2, including transmembrane serine protease 2 (TMPRSS2), sialic acid and extracellular matrix metalloproteinase inducer (CD147, also known as basigin).[6] SARS-CoV-2 can also directly infect engineered human blood vessel organoids *in vitro*.

During homeostasis, the endothelium, surrounded by mural cells (pericytes), maintains vascular integrity and barrier function. It prevents inflammation by limiting EC-immune cell and EC platelet interactions and inhibits coagulation by expressing coagulation inhibitors and blood clot lysing enzymes and producing a glycocalyx (a protective layer of glycoproteins and glycolipids) with anticoagulation properties.

An established feature of severe COVID-19 is the activation of coagulation pathways in a process called immunothrombosis, with potential development of disseminated intravascular coagulation (DIC). This is also related to EC activation and dysfunction because the disruption of vascular integrity and EC death leads to exposure of the

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thrombogenic basement membrane and results in the activation of the clotting cascade. Moreover, ECs activated by IL-1β and TNF initiate coagulation by expressing P selectin, von Willebrand factor and fibrinogen, to which platelets bind. Those cytokines were found to be significantly elevated in patients with COVID-19.

These cytokines promote release of ultra large Von Willebrand Factor (VWF) multimers, production of thrombosis factor (TF) and FVII/FVIIa leading to increased thrombin generation, and decreased levels of endogenous anticoagulants such as tissue factor pathway inhibitor (TFPI), antithrombin, and activated protein C. The extensive interplay between endothelial cells, platelets, monocytes (Mø), Polymorphonuclear neutrophils (PMNs), the complement system and the coagulation system result in a hypercoagulable state with increased levels of procoagulants, decreased levels of anticoagulants, and depressed fibrinolysis.[7]

In turn, ECs release trophic cytokines that further augment platelet production. Platelets also release VEGF, which triggers ECs to upregulate the expression of tissue factor, the prime activator of the coagulation cascade, which is also expressed by activated pericytes. In response, the body mounts countermeasures to dissolve fibrin-rich blood clots, explaining why high levels of fibrin breakdown products (D-dimers) are predictive of poor patient outcome. As a result of the DIC and clogging/congestion of the small capillaries by inflammatory cells, as well as possible thrombosis in larger vessels, lung tissue ischemia develops, which triggers angiogenesis and potential EC hyperplasia.[8] Perhaps similar mechanisms are present in the circulation of the lower and upper extremities.

Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis. Induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homoeostasis.

Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischemia, inflammation with associated tissue oedema, and a procoagulant state.[4]

The Renin Angiotensin Aldosterone System (RAAS) is linked to the coagulation cascade and may exacerbate the process of immunothrombosis, driving microthrombi formation in COVID-19.

First, angiotensin II (AngII) induces TF and Plasminogen activator inhibitor (PAI-1) expression by endothelial cells *via* the angiotensin 1 (AT1) receptor, contributing to a PAI-1/tPA (tissue plasminogen activator) imbalance and a hypercoagulable state associated with better prognosis in patients with severe COVID-19.This may explain why unresolved fibrin deposits are observed contributing to a PAI-1/tPA imbalance and a hypercoagulable state associated with better prognosis in patients with severe COVID-19. In contrast to the poor outcome in patients with high D-dimer. Multiple studies demonstrate evidence of coagulation dysfunction in patients with COVID-19 and its association with poor prognosis. The non-survivors had significantly higher D-dimer and fibrin degradation products levels as well as longer prothrombin time and activated partial thromboplastin time than survivors on admission.[9]

A meta-analysis was conducted by Xiong *et al.* which indicated that prothrombin time and D-dimer levels were significantly higher in patients with severe COVID-19 than in those with the mild disease. Future studies should aim to discover more biomarkers of severe cases of COVID-19, and studies exploring the underlying mechanism of deranged coagulation function in COVID-19 are urgently needed. The hemostatic system might be explored for underlying treatment against Coronavirus.[10]

Hyperinflammation and detrimental immunothrombosis may be central to the pathophysiology of COVID-19. Platelet hyperreactivity, hypercoagulability, hypofibrinolysis, complement overactivation, and RAAS derangement in the presence of underlying inflammatory-induced endothelial dysfunction likely led to a state of COVID-19-induced coagulopathy.[7]

Prevalence

Prevalence of thrombosis among patients with COVID-19 is not fully established but vascular surgeons should be aware of it. Most of the literature focuses on hospitalized patients.[9] Reported vascular events predominantly appear on the venous territory. Lodigiani *et al*. reported prevalence of venous thromboembolisms in 4.4%, ischemic strokes in 2.5%, acute coronary syndrome in 1.1%, in the Hospital of Milan, Italy, with a higher rate in patients in the Intensive Care Unit (ICU).[11] Thromboembolic risk seems to be higher in severe infections because of major inflammation and the need of an ICU.[12] Thus, in the study by Klok *et al*.,[5] the cumulative incidence of a composite outcome of vascular events (acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarc-

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tion, systemic arterial embolism) was 31%, the incidence of venous thromboembolisms was 27%, and the incidence of arterial events was 3.7%, among patients in the ICU.

Clinical presentation

In the last year there have been numerous reported cases and case series of acute arterial lower limb thrombosis, even in patients without severe artherosclerotic lesions and concomitant diseases. It seems that the link between all these patients and their ALI is the underlying COVID-19 infection and its pathological effects on the vessel wall. The vicious cycle could in fact result in thrombosis of a main large arterial vessel followed by symptoms of ALI. When there is atherosclerosis and peripheral arterial disease (PAD) present there is enough time for a collateral circulation to develop *via* a process called angiogenesis. In those circumstances acute thrombosis of a main vessel can manifest itself with fewer symptoms and milder clinical presentation. In the opposite scenario seen in COVID-19 cases in which there is lack of such collateral circulation to compensate the arterial inflow, the clinical manifestation is more severe. The risk of limb-loss is expected to rise dramatically. Swift and systematic approach should be the behavior of choice of the vascular surgeon as the European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines. It suggests that patients with ALI are not admitted primarily to vascular specialists. However, after thorough clinical work up by any competent doctor, the diagnosis of ALI is usually made easily. Early diagnosis is important in order to save time and increase the chance of limb salvage and successful treatment.[13]

The clinical presentation of ALI depends on the location and duration of the arterial occlusion, the presence of collateral circulation, and the metabolic changes related to tissue ischemia. Typically, after occlusion of a native artery, the signs of ischemia are located one level/joint distal to the level of occlusion. Every minute after the onset of symptoms is important because irreversible changes occur in the tissues such as nerve damage (plegia and paralysis), skin bullae which may progress from difficult to heal necrosis, sludge phenomena in the microcirculation of the most distal parts of the limb. Low blood oxygen saturation caused by the main target of the virus the lungs also play a role in worsening the ischemia of the limb. All of the above could potentially lead to minor or major tissue damage and inevitable amputation.

Arterial complications take various forms. Multiple reports were published recently with various clinical presentations. In children, COVID-19 is commonly asymptomatic, but a Kawasaki-like syndrome is described.[14] In adults, Vulliamy *et al*. detailed acute aortoiliac and mesenteric arterial thrombotic occlusions in a 60-year-old patient and a 75-year-old patient, respectively, while another case of acute aortic thrombosis was described in association with pulmonary embolism in a 71-year-old woman.[15, 16] Acute ischemic stroke secondary to common carotid artery thrombosis or in a prothrombotic state (leukemia) has also been reported.[17] Finally, limb arteries can be affected in elderly patients and in pathological situations: upper limb ischemia in a 71-year-old diabetic man and lower limb ischemia complicated by distal cutaneous embolism in a 71- year-old aged patient with severe COVID-19.[18, 19] Veyre *et al*. presented a femoral artery thrombosis in a 24-year-old adult without medical history and a negative etiological assessment except nonsevere COVID-19. The treatment was standardized, using aspirin, low molecular weight heparin (LMWH), and thrombectomy.[20]

When comparing COVID-19 with non-COVID-19 patients, significant differences were observed only in the proportion of patients with chronic obstructive pulmonary disease. Nevertheless, COVID-19 patients tended to have a lower cardiovascular risk profile. On the other hand, this group showed significantly higher inflammatory markers than the non-COVID-19 cohort and higher mortality during hospital admission.[21]

Diagnosis

Clinical examination: the classic “six Ps” (pain, pallor, pulselessness, poikilothermia [perishing with cold], paresthesia, and paralysis) can help to appreciate the clinical severity of ischemia. However, in clinical practice all six signs are rarely encountered, unless there is a severe ALI in a patient with otherwise normal arteries. Detection of peripheral pulses is enhanced by determination of the ABI using handheld Doppler. ABI in ALI is also a predictor of outcome and an index <0.7 is critical. The loss of sensory and motor function are symptoms of a threatened limb with a need for immediate revascularization. The Rutherford classification for ALI is the most commonly used to determine whether the limb is viable, threatened, or irreversibly ischemic, and to guide clinical management (Table I). It is important that both legs are examined to exclude bilateral disease and to look for bilateral conditions such as popliteal artery aneurysm (PA). Physical examination should also include all other peripheral pulses and looking for signs of visceral ischemia (abdominal tenderness). Patients with neurological impairment or deep venous thrombosis may have clinical signs and symptoms similar to ALI. Those

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TABLE I.—*Clinical categories of acute limb ischemia according to Rutherford.*

Grade	Category	Sensory loss	Motor deficit	Prognosis	Doppler signals	
					Arterial	Venous
I	Viable	None	None	No immediate threat	Audible	Audible
IIA	Marginally threatened	None or minimal (toes)	None	Salvageable if promptly treated	Inaudible*	Audible
IIB	Immediately threatened	More than toes	Mild/moderate	Salvageable if promptly revascularized	Inaudible	Audible
III	Irreversible	Profound, anesthetic	Profound, paralysis (rigor*)	Major tissue loss amputation. Permanent nerve damage inevitable	Inaudible	Inaudible

*In the original 1997 classification it was stated that arterial Doppler sounds are never present in stage IIA, and that rigor (mortis) is always present in stage III. However, it is the opinion of the Writing Committee that exceptions to these rules do exist, and a slight modification of the Rutherford classification from 1997 may be appropriate in the future.

should be distinguished using the wide variety of imaging technologies that modern medicine provides. Given the cardiac origin of embolic occlusions, a focused cardiac examination should be performed, without interfering with or delaying the treatment of ALI.[13]

An increased D-dimer appears to be both diagnostic and prognostic factor given that all the reported cases have severely elevated levels of the lab result, hence why the vascular surgeon should take it in consideration.

The time needed to obtain any type of imaging should be weighed against the urgency of revascularization. If noninvasive imaging is chosen, it is important that this does not delay subsequent treatment. The easiest and cheapest imaging modality is duplex doppler sonography. But unfortunately, it is operator dependent. Given the fact that COVID-19 patients are very difficult to transport between hospitals, this diagnostic tool is appropriate to consider for primary diagnosis. It can be used as an imaging modality in order to rule out arterial occlusion, but the diagnostic accuracy is lower for detection of stenoses or occlusion in the tibial arteries or in some other cases like obese patients for example. In terms of diagnostic accuracy, angiography is still considered as the best option. Unfortunately, in unstable COVID-19 patients, performing an angiography is a challenge because of two main reasons. Firstly, the angiography is time consuming and requires patient compliance. Furthermore, some patients suffer severe respiratory deficiency and could not tolerate supine position for a long time. In these cases, CT angiogram (CTA) should be performed. Most modern hospitals can offer expedited CTA. Current CT technology allows coverage of the entire body in a single examination, with short acquisition times and high resolution.

Treatment

Patients with ALI should be treated by specialists in vascular and endovascular therapies, in centers with a full range of facilities to manage patients with vascular diseases. This may mean that a patient will need to be transferred from a non-vascular center for treatment, if appropriate. The urgency of transfer will depend on the severity of the ischemia, with patients with motor or sensory loss (Table I) requires urgent transfer.[13]

That is not always the case in the light of COVID-19 pandemic. A transfer could be risky and extremely challenging as most of the severe cases require intensive care. On top there is high risk of spreading the disease among the medical personnel and other patients. The strategy employed will depend on a number of factors, including the expertise and facilities of the treating team, and patient factors such as the duration and severity of ALI, the location and cause of the occlusion, comorbidities, and therapy related risks. There is a difficult tradeoff between the cost of delay, when a patient is transferred, and the limited expertise that may be available in the local hospital where the patient presents.

It is possible that unprecedented stressors on the healthcare system, particularly at the epicenter of the pandemic at its peak, may have indirectly contributed to negative treatment outcomes, for example by delaying the patient's presentation following the onset of symptom.[22]

The standard recommended medical treatment of ALI includes appropriate analgesia and intravenous administration of unfractionated heparin (UFH): initially 5000 IU, or 70e100 IU/kg, followed by infusion, dose adjusted to patient response, and monitored by activated clotting time or activated partial thromboplastin time (APTT). The aim was to reduce further embolism or clot propagation, and to provide an anti-inflammatory effect. Although this approach is widely accepted, no recent randomized study has been done to confirm the benefit of UFH for ALI, nor has any randomized study compared unfractionated UFH with other anticoagulants and in that manner an approach specifically designed for the COVID-19 patients. In patients

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with confirmed or suspected heparin induced thrombocytopenia, non-heparin anticoagulants such as lepirudin, argatroban, or danaparoid are options. Advice from a hematologist may be valuable. Other measures that may be beneficial in patients with ALI include intravenous hydration and supplementary oxygen and lowering the foot end of the bed (anti-Trendelenburg position).[13]

To choose the best treatment approach in a patient with ALI, the degree of ischemia and vitality of the limb should be assessed in accordance with the available clinical classifications.

The available guidelines are written in the context of the most common causes: embolism, thrombosis of native arteries or reconstructions, peripheral arterial aneurysm, dissection, and traumatic arterial injury. The ischemia is graded clinically according to the Rutherford ALI classification system (Table I). Assessment determines whether the limb is viable or irreversibly damaged. The distinction between grade IIa and IIb, and between grade IIb and III, can sometimes be challenging. Prompt diagnosis and revascularization by means of catheter-based thrombolysis and/or thrombaspiration or by open surgery reduces the risk of limb loss and death. Primary amputation is recommended in patients with irreversible (class III) ischemia. Despite urgent revascularization, mortality and major amputation rates are high.

At the time of writing this article there is no guideline regarding COVID-19 induced ALI.

Since its introduction in 1962 by Fogarty, balloon thrombo-embolectomy has remained the standard treatment of ALI caused by embolic occlusion, particularly when dealing with occlusion of an otherwise normal artery. However, this is an increasing rarity in modern surgical practice, as most patients with atrial fibrillation (AF) receive oral anticoagulation. Nevertheless, some of them could have co-existing vascular disease.

For patients with Rutherford grade IIa acute limb ischemia is recommended that (percutaneous) catheter-directed thrombolysis (CDT) is considered as an alternative to surgery.[13]

Most of the available publications address thrombolysis as a treatment of choice in patients with COVID-19 induced venous embolization followed by pulmonary embolism.

There are vascular centers that successfully used catheter directed thrombolysis CDT in arterial thrombosis. Mohammad *et al.* used this therapeutic modality in a 49-year-old man with eccentric mural thrombus at the aortic bifurcation, extending into left common iliac and an abrupt occlusion of left popliteal, tibioperoneal, and posterior tibial arteries. At six-week follow-up, he showed full recovery.[23] Other physicians choose more conservative approaches.

Gonzalez Cañas *et al*. report three patients with no history of peripheral arterial occlusive disease, admitted for severe COVID-19 with acute limb ischemia and femoro-popliteal occlusion associated with intra-aortic thrombus. A histology sample was taken, and it showed inflammatory cells such as polymorphonuclears, T-lymphocytes, histiocytes, macrophages and multinucleated giant cells, in the thrombi and all layers of vessels, associated to endothelial proliferation and angiogenesis with a variable degree of collagen deposition and myofibroblastic proliferation. They consider full-dose anticoagulation with LMWH as first-line treatment option. Other anti-inflammatory agents (anticytokine drugs, ACE inhibitors or statins) might be used. A suggestion is made regarding open surgery in favor over endovascular procedures when medical treatment fails. Any delay in diagnosis and/or treatment may lead to increased morbidity, including limb loss.[24]

COVID-19 seems to lead to unexpected arterial complications even in the otherwise healthy population.

Baccellieri *et al*. reported a case in June 2020 regarding a 67-year-old male patient with no past medical history with confirmed COVID-19 infection and complete occlusion of the iliac and femoro-popliteal arteries. An emergent thrombectomy was performed with a satisfactory result but with persistent acroischemia of the lower extremities on 6th postoperative day.

The authors advocate the use of UFH as a therapeutic over the administration of LMWH. Furthermore, anticoagulation cannot be managed as one-size-fits-all owing to the coexistence of several “sheds of thrombophilia” (*i.e.* heparin resistance [HR], deficiency of antithrombin III [ATIII]); third, the aPTT should be integrated with the monitoring of the anti-Xa activity levels to prevent overdose.[25]

Another team reports a similar case of a 77-year-old male patient with a thrombus within the mid left superficial femoral artery and occluded left anterior tibial artery, left posterior tibial artery, and left peroneal artery with no flow to the foot. He was put on therapeutic anticoagulation with heparin and underwent a thrombectomy of left common femoral artery, profunda femoris, superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery.[18]

An otherwise healthy patient was reported by Veerasuri *et al*. He was 56-year-old male, non-smoker, with no

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significant past medical history presenting with elevated D-dimer and bilateral acute limb ischemia due to thrombosis. Arterial duplex study showed proximal short segment right superficial femoral artery (SFA) and popliteal trifurcation occlusion with echolucent homogenous thrombus. He also had left popliteal trifurcation occlusion as well. An unusual decision was made for the patient to be managed conservatively with Rivaroxaban. In two months, the authors reported a presence of echolucent homogenous thrombus in both lower limbs similar to the initial scan. However tiny channel of flow. They continued to manage him conservatively.[26]

As more research on the topic is being made, we can assume that despite anticoagulation, a high number of patients with COVID-19 ARDS developed life-threatening thrombotic complications, meaning that higher anticoagulation targets than in usual critically ill patients should probably be considered. There also seems to be a strong association between high D-dimers and thrombosis but further research is needed.[27]

The American Society of Hematology (ASH) recommends that all hospitalized patients with COVID-19 should receive pharmacological thromboprophylaxis with low-molecular-weight heparin or fondaparinux unless there is a bleeding risk and states that there is no role for full therapeutic-intensity anticoagulation unless there is an indication. Such indication could be patients with known severe thrombophilia or another hypercoagulable state, patients with PAD and existing bypass reconstruction.

The intimate association between inflammation and thrombosis would suggest an anti-inflammatory/antiviral therapeutic approach should be considered in parallel to anticoagulation. Furthermore, as the fibrinolytic potential of blood from patients with COVID-19 is extremely low, even with anticoagulation, immediate consequences of thrombus may not be treated and may just be preventing further thrombus.[28]

Currently there is no treatment protocol available. The decisions regarding anticoagulation prophylaxis are left in the hands of the vascular specialists. The latter could lead to potentially negative outcomes due to the unexpected complications in each individual patient. One of the worst nightmares of each vascular surgeon is to find out that after a successful thrombectomy of an arterial segment there is a sudden rethrombosis due to inadequate anticoagulation. Such events usually lead to even worse symptoms than the initial ones. Considering the clinical and angiographic characteristics as well as the high failure rate in these patients, most of the vascular surgery departments perform a more aggressive strategy in regard to COVID-19 induced ALI.

As a large study performed in New York City states, the mortality rate was significantly higher in patients suffering thrombotic events (both venous and arterial) which supports the aggressive strategy regarding the complications arising from the infection.[29]

Indes *et al.* presented a single-center retrospective cohort study. With retrospective case control design, they identified and evaluated potential risk factors for arterial thromboembolic disease in SARS-CoV-2 positive patients. During the study period, 424 patients underwent diagnostic imaging. Forty patients were recognized with arterial thromboembolism. The overall number of positive patients was 15. They observed that these patients tended to be younger (64 years of age *vs.* 70 years of age, P=0.027 and more frequently male (66.7% *vs.* 40.0%, P=0.191). The team noted that the smokers were less frequently (42.9% *vs.* 68%). Patients who were SARS-CoV-2 positive had a much lower rate of any antiplatelet use (21.4% *vs.* 62.5%, P=0.035). The positive patients with arterial thrombosis had a higher mortality rate (40.0% *vs.* 80.0%, P=0.041) They were treated successfully with open surgical thrombectomy in six cases (40%), anticoagulation alone in four cases (26.7%) or were not treated in five patients (33.3%). According to the anatomic thrombus distribution, there were significantly more SARS-CoV-2 positive patients with aortoiliac involvement compared to the non-COVID or non-tested group (33.3% *vs.* 4.0%, P=0.040). They observed less tibial/pedal (13.3% *vs.* 40.0%, P=0.154) and more upper extremity (20.0% *vs.* 8.0%, P=0.537) involvement in the positive patients. Furthermore Indes *et al.* documented the severity of disease on presentation. Most of the patients (60%) with arterial thrombosis had critically severe disease. Only 3 patients were asymptomatic (20%).[30]

Surgical outcomes

Emergent thrombectomy is the treatment modality giving the patient best chances of limb salvage. Even though, most of the reports so far have poor outcomes mainly as a result of heparin resistance, and the overall pro-inflammatory state of the patients. Rethrombosis seems to be common and vascular surgeons should be extremely cautious in the postoperative period management of such patients.

Perini *et al.* presented two cases of ALI secondary to thrombosis in young and active patients with no comorbidities and confirmed COVID-19 pneumonia. Both patients had D-dimer concentrations higher than 9000 ng/mL.

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One of them underwent emergent thromboembolectomy through femoral cutdowns, with bilateral pedal pulse recovery. However, thrombosis reoccurred approximately 2 hours after the thromboembolectomy, and the patient died on postoperative day two.[31]

In the previously mentioned cases reported by Gonzalez *et al*. there was one patient who underwent above-knee amputation performed after unsuccessful endovascular treatment with mechanical percutaneous thrombectomy of popliteal artery, thrombolytic therapy and balloon angioplasty.

The other underwent a femorotibial bypass with autologous for clinical worsening with ischemic ulcers on right foot.[24]

Kashi *et al*. published a case series with 6 cases. Only one of them underwent thrombectomy followed by amputation.[32]

If the pandemic situation continues to get worse, in the near future we can expect the number of unsalvageable limbs to increase leading to a rise in the cases of both minor and major amputations.

The results from a retrospective study conducted in New York seem in favor of the statement that adjusted for history of peripheral vascular disease, death or limb amputation is more common in patients with COVID-19 infection. All of their patients with COVID-19 infection who underwent lower extremity CTA had at least one lower extremity clot (100%) while only 69% of controls had clots. Their mean clot score for lower extremity vessels in patients with COVID-19 was greater than that of propensity score matched controls (those without COVID-19 infection. They concluded that COVID-19 is in fact associated with lower extremity arterial thrombosis characterized by greater clot burden and more dire prognosis.

Another takeaway from this study is the statement that greater arterial thrombus burden may be a marker of mortality by itself, but it can also be attributed to the aggressive nature of the COVID-19 disease, which has been associated with cytokine storm, fulminant myocarditis and atypical hypercoagulability despite patients being on therapeutic anticoagulation.[22]

There is no validating scoring system for calculating arterial clot burden in the lower extremities. Goldman *et al*. suggested three different systems to perform this task. Vessels were categorized in three zones: aortic (thoracic and abdominal aorta), proximal (common iliac arteries, external iliac arteries, common femoral arteries, superficial femoral arteries and popliteal arteries) and distal (crural arteries). Arteries of the foot were not assessed. Their study demonstrated an association between COVID-19 and lower extremity arterial thrombosis with greater thrombus burden characterized by predilection for proximal arteries. Additionally, the incidence of death and amputation is significantly more common in COVID-19 patients especially if there were systemic or respiratory symptoms and presentation.[22]

There are reports suggesting that when surgical intervention is done in a timely manner, it can bear positive results and complete recovery. Mestres *et al*. report four cases of COVID-19 arterial thrombosis. Two of those patients underwent surgery. One patient had undergone open bilateral popliteal direct thrombectomy of all distal vessels and one had undergone open femoral-popliteal and radial-ulnar thrombectomy. Both patients recovered immediate patency of all declotted arteries and experienced improved clinical symptoms, despite the finding of segmental distal asymptomatic rethrombosis at 24 hours after surgery.[19]

Thrombosis of different arteries seems to be significantly more frequent among COVID-19 patients. Of 38 COVID-19 patients reported by Rey *et al*., 11 showed simultaneous thrombosis of different locations (7 had multi territory ischemic stroke, 3 acute lower limb arterial ischemia due to occlusion of the terminal aorta, and 1 patient had an infarction with thrombus in 2 different coronary arteries). Interestingly, only 1 of them had a history of atherosclerosis (coronary artery disease) and 3 of these patients also had venous thromboembolic disease (2 of them pulmonary embolism and 1 deep vein thrombosis). They summarized that hospitalized patients with COVID-19 have a significant risk of acute arterial thrombosis. Significantly higher mortality and more frequent simultaneous thrombosis of different arteries were observed in these patients than in non-COVID patients. Clinicians managing these patients should maintain a high level of suspicion and lower thresholds for appropriate testing when clinically indicated.[21]

Large to mid-size arteries in the upper limb are not spared by the disease. Kaur *et al.* report a 71-year-old Hispanic male with a past medical history of diabetes mellitus. On day 5 of hospitalization, the patient reported sudden onset severe pain in the right arm. Computed tomography showed a non-occlusive thrombus of the right brachiocephalic trunk, occlusive thrombus with the axillary artery with reconstituted flow in the diminutive brachial artery extending to the radial, proximal ulnar and interosseous arteries, and incomplete visualization of the distal ulnar artery. The patient was started on therapeutic anticoagulation with unfractionated heparin and underwent open thromboembolectomy of the right brachiocephalic, subclavian, axillary, brachial, radial, ulnar arteries and endar-

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terectomy of the right brachial artery. Post embolectomy, the patient had palpable right radial and ulnar pulses with normal sensation and motor function.[9]

A single center observational cohort study showed that thromboembolectomy was performed in 64.7% of their patients with COVID-19 associated ALI. The rest of their patients underwent other types of surgical treatments. Overall, limb salvage was obtained in 93.3% patients: major amputation was needed in 1 patient.[33]

In contrast a retrospective study was conducted in 7 hospitals within Northwell Health, the largest academic health system in New York State, serving approximately 11 million people. It represents an in-depth result on 49 patients with acute arterial thromboembolisms and COVID-19. Eighty three percent of these patients had elevated D-dimer levels greater than 1,000 ng/mL. Thirty-five of those patients were treated surgically and the rate of limb loss was 18%, and overall, in-hospital mortality was 46%. Mortality in patients with lower limb ischemia was 50%.[34]

Whether or not there is a strong correlation between D-dimer levels and successful limb salvage is yet to be determined. Most of the data so far comes from small retrospective studies and case reports.

It seems that there is a correlation between comorbidities with hypertension and diabetes being the most common ones and negative treatment outcome as suggested by a single-center retrospective review of patients presenting with ALI and an active diagnosis of COVID-19 pneumonia. Of these patients, the mean age was 62 years, and peak D-dimer level during hospitalization was 4695 ng/mL. Out of 10 patients without previous peripheral vascularization, four underwent one and only two were successful. Overall, 30-day mortality was 40%, with one death occurring in a patient who underwent revascularization. Major lower extremity amputations were performed in two (20%) patients and four (10%) limbs.[35]

In addition, vascular surgeons should be aware of the potential complications of the virus due to prosthetic graft thrombosis as reported by Giacomelli *et al*. A 67-year-old male with confirmed COVID-10 infection who had undergone open repair of an abdominal aortic aneurysm with bifurcated aorto-bi-iliac Dacron graft developed complete thrombosis of the aortic graft without detectable blood flow at the femoral level.[36]

Conclusions

This review of literature reveals that healthcare providers should be aware of the manifestations of COVID-19 and a high index of suspicion should be maintained so that all can benefit from evidence of measures that have been found to be effective. Although previous reports also identified COVID-19 patients with limb ischemia, there are limited data on the clinical course and treatment. An aggressive and timely medical therapy and surgical interventions should be performed to obtain positive treatment outcomes. Nevertheless, the absence of evidence-based protocols remains an obstacle for healthcare providers. Further quality research about SARS-CoV2 infection with a focus on arterial thrombotic complications are needed to characterize arterial consequences of Coronavirus and to evaluate the necessity of therapeutic anticoagulation in COVID-19 patients with peripheral arterial occlusive disease or thrombophilia.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Bistra P. Boneva and Boris N. Ilchev have given substantial contributions to study conception and design, Margaret P. Dimova, Nadelin K. Nikolov and Boyka I. Stoyanova to data acquisition, analysis and interpretation, Bistra P. Boneva, Margaret P. Dimova, Nadelin K. Nikolov, Boyka I. Stoyanova and Boris N. Ilchev to manuscript writing, Bistra P. Boneva and Boris N. Ilchev to manuscript critical revision. All authors read and approved the final version of the manuscript.

History.—Manuscript accepted: July 30, 2021. - Manuscript received: March 15, 2021.